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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/730,374	12/05/2000	John A. Lust	150.188US2	7446

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 11/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/730,374	Lust et al.
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 15, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above, claim(s) *14 and 16* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-13, 15, 17, and 18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment and submission of a supplemental sequence listing in paper form and CRF received on 8/20/02 in response to the notice to comply mailed on 7/15/02 has been entered. Applicant's response to the restriction requirement received on 5/6/02 has also been entered. Claims 1-18 are pending in the instant application. Claims 14 and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9. Claims 1-13, 15, and 17-18 are currently under consideration in the instant application. An action on the merits follows.

Nucleotide and/or Amino acid Sequences

Applicant's supplemental sequence submission and amendment to the specification places this application in compliance with 37 CFR 1.821-1.825.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-11, 13, and 15 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that it wouldn't place an undue burden on the

examiner to rejoin groups the groups, in particular groups I and II. Applicant's arguments are found persuasive in regards to the claims of group II, i.e. claims 12, 17, and 18. However, applicant's arguments are not persuasive in rejoining group III with groups I and II. The nucleic acids of group III are unrelated to the DNA sequences of the claims in Group I, and further can be used for substantially different purposes than making the protein of Group II, e.g. use in hybridization assays, PCR, etc. Likewise, the protein can be made without the nucleic acid by chemical synthesis. Thus, restriction between the subject matter of combined Groups I and II and the subject matter of Group III is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8, 10, 12-13, and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to a fusion protein comprising a polypeptide which specifically binds CD38. The specification does not provide a

written description for any CD38 binding polypeptides which are not antibodies or fragments thereof. The specification provides a description of isolated monoclonal antibodies which are specific for CD38 and describes methods of preparing single chain antibodies and humanized antibodies. However, the specification lacks guidance concerning the identity and chemical composition of any polypeptide other than an antibody which binds specifically to CD38.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). In the absence of any description of actual non-antibody CD38 binding proteins or nucleic acids encoding a non-antibody CD38 binding protein, the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins which may be capable of binding to CD38, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. The nucleic acid itself is required. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Therefore, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for CD38 binding polypeptides

which are not antibodies. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-13, 15 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The applicant claims methods of treating multiple myeloma by administering a composition comprising a fusion polypeptide comprising a polypeptide which binds to CD38 linked to a polypeptide which binds DNA and a DNA sequence which encodes a cytotoxic agent, and a pharmaceutical or therapeutic composition capable of inhibiting tumor cell growth comprising a fusion polypeptide comprising a polypeptide which binds to CD38 linked to a polypeptide which binds DNA either alone or in combination with a DNA sequence which encodes a cytotoxic agent

The specification fails to provide an enabling disclosure for making a fusion polypeptide which includes a CD38 binding polypeptide which is not an antibody. As noted above in the rejection these claims for lack of written description, the specification fails to teach, describe, or identify any polypeptide which is not an antibody that binds to CD38. In the absence of such description, the skilled artisan would not be able to make a non-antibody CD38 binding polypeptide fusion protein according to the instant invention without undue experimentation.

The specification further fails to provide an enabling disclosure for targeting CD38+ cells, including multiple myeloma cells in vivo, using the disclosed fusion proteins by themselves or complexed with plasmid DNA. The specification alleges that the administration of the disclosed CD38+ fusion protein complexed with a DNA plasmid encoding a cytotoxic agent can result the specific targeting of the plasmid DNA to CD38+ cells in vivo, in particular CD38+ tumor cells. The specification further teaches that once the complex binds to the target cell, the complex is internalized and the cytotoxic gene of interest is expressed in the target cells leading to cell death. The specification's working examples are limited to *in vitro* experiments which demonstrate the preparation of a scFv antibody which specifically binds CD38 and which is internalized by CD38+ tumor cells in a tissue culture assay. The specification does not provide any concrete data regarding any actual fusion polypeptide comprising the scFV and protamine or any other DNA binding polypeptide, or provide any evidence that the hypothetical scFV fusion protein discussed in the specification, either by itself or complexed with a plasmid DNA as depicted in Figures 4 and 5, is effectively internalized by CD38+ cells. The specification's teachings regarding the claimed compositions is purely prophetic. The specification fails to provide sufficient guidance for routes and sites of administration, dosages of the complexed vectors, and level of toxin gene expression required to effectively treat or inhibit multiple myeloma , primary amyloidosis, monoclonal gammopathy, or acute myeloid leukemia *in vivo*. Particularly in regards to route and site of administration, the specification fails to provide sufficient guidance concerning the delivery of a

targeting complex which has been locally administered to target cells located at a distance from the site of injection.

The art at the time of filing proposed the use of immunotoxins to treat various conditions such as cancer. However, a major problem associated with the delivery of immunotoxins in vivo is their immunogenicity and toxicity. Delivery of foreign protein rapidly triggers natural immunity resulting in clearance of the foreign protein. For xenogeneic proteins, prexisting antibodies are often present which act quickly to clear the xenoantigens. In regards to the specific treatment of CD38+ tumors, such as multiple myeloma, the art teaches that the administration of an immunotoxin comprising an anti-CD38 antibody to patients with myeloma resulted in the generation of HAMA and toxicity induced episodes of blindness leading to the discontinuation of the treatment (Maloney et al. (1999) Sem. in Hematol., Vol. 36 (1), 30-33, page 30). The art does not report that an any effect on the myeloma was achieved using this strategy. In addition, the art at the time of filing also teaches that the targeted delivery of nucleic acids to specific cells or tissues in vivo was considered highly unpredictable. Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting

has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). As discussed above, the specification fails to provide guidance in the form of detailed teachings or specific working examples for overcoming any of these obstacles to successful treatment of CD38+ tumors with applicant's disclosed targeting compositions.

Therefore, in view of the art recognized unpredictability in targeting nucleic acid vectors to specific cell populations *in vivo*, the lack of guidance provided by the specification for routes of administration, dosages, etc. which correlate with any therapeutic effect on multiple myeloma or acute myeloid leukemia, the lack of *in vivo* or *in vitro* working examples which demonstrate specific targeting of the disclosed antibody/DNA complex to CD38+ cells and expression of the encoded cytotoxic genes, the art recognized toxicity of anti-CD38 fusion proteins *in vivo* in patients, and the breadth of the claims, it would have required undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13, and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/22618, 10/24/95, hereafter referred to as Marasco et al. in view of Goldmacher et al. (1994) Blood, Vol. 84 (9), 3017-3025, Ellis et al. (1995) J. Immunol., Vol. 155 (2) 925-937, and Donovan et al. (1997) Blood, Vol. 90 (10), 386. The applicant claims a pharmaceutical or therapeutic composition capable of inhibiting tumor cell growth comprising a fusion polypeptide comprising a polypeptide which binds to CD38 linked to a polypeptide which binds DNA either alone or in combination with a DNA sequence which encodes a cytotoxic agent. The applicant further claims said compositions wherein the CD38 binding polypeptide is an antibody, or an antibody derived from the HB7 hybridoma, or a humanized antibody, or an scFV antibody, or wherein the CD38 binding peptide is linked to a radioisotope. The applicant also claims said compositions wherein the DNA binding polypeptide is protamine, wherein the cytoxic agent is

diptheria toxin or pseudomonas exotoxin, and wherein the transcription unit is B cell, T cell, or myeloid specific promoter. Please note that the intended use of the compositions for "therapeutic" or "pharmaceutical" use is not given patentable weight. It is noted that the use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

Marasco et al. teaches methods of transforming a target cell comprising contacting a target cell with a composition comprising a single chain antibody (scFv) or Fab portion of an antibody which binds to a site on a target cell linked to a DNA binding protein such as protamine further complexed with a nucleic acid encoding a cytotoxic protein such as Pseudomonas exotoxin operably linked to a viral or cell specific promoter (Marasco et al., pages 44-46, claims 1-16, especially claims 4, 8, 9 , and 12). Marasco et al. further teaches the use of humanized antibodies to target cells (Marasco et al., pages 13 and 23). Marasco et al. further provides motivation for targeting tumors with said compositions by teaching that the use of the disclosed DNA-immunoconjugates allows the delivery of cytoxic genes to target cells such as tumors with the immunogenicity/toxicity problems associated with tradition immunotoxins (Marasco et al., pages 5, 8-9, and 13). Marasco et al. also provide motivation for choosing antibodies which target

cell surface receptors which are present in large amounts on certain tumors (Marasco et al., page 13, first paragraph).

Marasco et al. differs from the instant invention by not teaching the use of an anti-CD38 antibody, either Fab, scFV, or humanized, in order to target CD38+ tumors, e.g. multiple myeloma. Goldmacher et al. teaches an anti-CD38 immunotoxin fusion protein for the treatment of multiple myeloma wherein the anti-CD38 antibody is derived from the HB7 hybridoma (Goldmacher et al., page 3017, abstract). Goldmacher et al. further teaches that the anti-CD38 immunotoxin targets CD38+ tumor cells (Goldmacher et al., page 3017). Thus, based on the motivation provided by Marasco to use antibodies which recognize a protein overexpressed on a tumor cells in their DNA-immunoconjugate and the motivation to use the DNA-immunoconjugate system to deliver toxins to tumor cells over traditional immunotoxins, it would have been *prima facie* obvious to the skilled artisan to use the anti-CD38 antibody taught by Goldmacher in the compositions and methods taught by Marasco et al. Further, based on the successful use of the CD38 antibody to target CD38+ cells, the skilled artisan would have had a reasonable expectation of success in making and using a composition comprising an anti-CD38 antibody linked to protamine and complexed with a plasmid encoding exotoxin.

As noted above, Marasco et al. teaches the use of humanized and scFV forms of an antibody as the targeting moiety of their disclosed composition. Goldmacher et al. teaches a Fab fragment of the HB7 antibody. Ellis supplements Goldmacher and Marasco by teaching a humanized anti-CD38 antibody which successfully targets and binds CD38 positive cells (Ellis et

al., page 925). Donovan et al. further supplements Goldmacher and Marasco by teaching a single chain anti-CD38 antibody which binds and is endocytosed by CD38+ multiple myeloma cells (Donovan et al., abstract 386). Based on the teachings and motivation provided by Marasco and Goldmacher above, it would have been *prima facie* obvious to use any of the anti-CD38 antibodies taught by Ellis, Donovan, and Goldmacher in the methods and compositions taught by Marasco et al. Further, based on the successful use of the antibodies taught by Donovan and Ellis to target CD38+ cells, the skilled artisan would have had a reasonable expectation of success in making and using a composition comprising an anti-CD38 antibody which is either humanized or an scFV linked to protamine and complexed with a plasmid encoding exotoxin.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER